Impact of Formulation Processes on Dosage Form Determination of Phytonadione Injectables

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T1130-06-34

PURPOSE

Phytonadione injection contains an oil-like immiscible drug substance, which is mixed with surfactant, then further dispersed in an aqueous phase. The Orange Book, product label, and USP monograph designated the dosage form of phytonadione injection using subtly different terminologies (injection, aqueous colloidal solution, and emulsion, respectively). Consequently, difference in dosage form necessitates different characterization and criteria for demonstrating equivalence. Furthermore, understanding the impact of manufacturing process conditions (e.g., stir rate, shear, mixing equipment, directionality) on formulation dispersion state and particle size distribution (PSD) is paramount.

OBJECTIVE(S)

The objectives of this study were to compare how different sources of polyethylene glycol (PEG)-n castor oil (surfactant) and manufacturing processes give rise to similarities/differences in key excipient properties and to determine the dosage form of the product.

METHOD(S)

Three formulations were produced in-house maintaining the same formulation composition with the exception of the type of polyethylene glycol (PEG)-n castor oil surfactants(n = 30, 35, and 40). Each formulation was mixed under varying processing conditions, ranging from low shear (via magnetic stirrer) to high shear mixing (via homogenizer) as well as differing mixing directionality, either dispersed oil phase into continuous aqueous phase (O2A) or continuous aqueous phase into dispersed oil phase (A2O). PSD of formulations were measured by batch mode dynamic light scattering (DLS) (Wyatt Technology, DynaPro Plate Reader II) and compared to PSD as determined by asymmetrical flow field-flow fractionation with online multiangle light scattering (AF4-MALS) and online DLS (Wyatt Technology, Eclipse). A commercially available phytonadione injection product was used for PSD comparison.

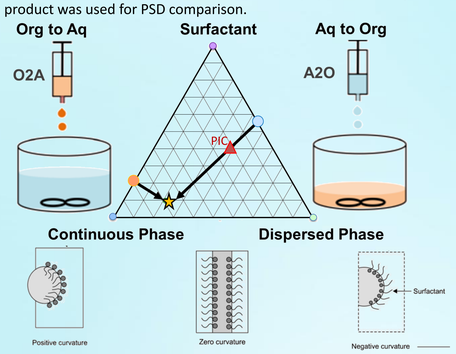

Figure 1. Diagram of formulation directionality, during processing in the A2O direction the mixture passes through a phase inversion composition (PIC) where the interface rearranges from water-in-oil (W/O) to oil-in-water (O/W) dispersion, the resultant PSD is strongly influenced by processing conditions (e.g., temperature, shear of mixing, etc.) during phase rearrangement.

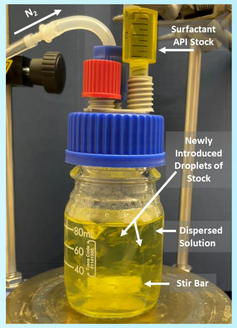

Figure 2. Experimental setup for preparation of phytonadione injection formulations at ambient temperature and under low shear.

RESULT(S)

- For all three PEG-n castor oils, although low energy preparation process (i.e., slow stirring at room temperature) readily produced a transparent homogeneous dispersion, further investigation on the manufacturing process (i.e., mixing, temperature, etc.) and formulation composition (surfactant to oil ratio, etc.) indicated that both can affect the initial intermediary dispersion state of the formulation (e.g., producing macro-, nano-, or micro- emulsions). All subsequent data presented here are for formulations using PEG-35-caster oil.
- For the formulation composition of phytonadione injection, varying processing conditions produced a spectrum of initial dispersion states (Figure 3).
- Notably, both appearance (turbidity) and more quantitatively PSD were found to be useful surrogates for distinguishing nanoemulsions (broad PSD, turbid) and microemulsions (monodispersed PSD, translucent) (Figure 5).
- Additional stability studies with varied storage duration and temperature further confirmed the phytonadione dispersion is ultimately a thermodynamically stabilized system, as opposed to a kinetically stabilized system.

CONCLUSION(S)

For the phytonadione injection composition, the nanoemulsion dispersion state represented a transient state for the system, which was limited by kinetic constraints like surfactant lability. With enough time and energy (thermal or mechanical) the phytonadione injection formulations reverted to the most energetically favored microemulsion dispersion state. Lastly, an interface directed pseudo-ternary phase diagram was constructed to elucidate the role of interfacial areas (e.g., via changes in manufacturing processes) on the dispersion states, which helped to explain the difference in the initial dispersion states of phytonadione formulations caused by switching the order of mixing continuous and dispersed phases. Based on the PSD of the inhouse produced samples as well as the employed processing conditions, phytonadione formulation is unlikely to be a kinetically stabilized emulsion. Instead, it appeared that phytonadione formulation is a thermodynamically stabilized system, such as microemulsions or micelles.

ACKNOWLEDGEMENTS

Drs. Smith and Liu were supported in part by the Oak Ridge Association of Universities (ORAU) and the Oak Ridge Institute of Science and Education (ORISE), through an agreement between the U.S. Department of Energy and the U.S. FDA.

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RESULTS: COMPOSITION EFFECTS

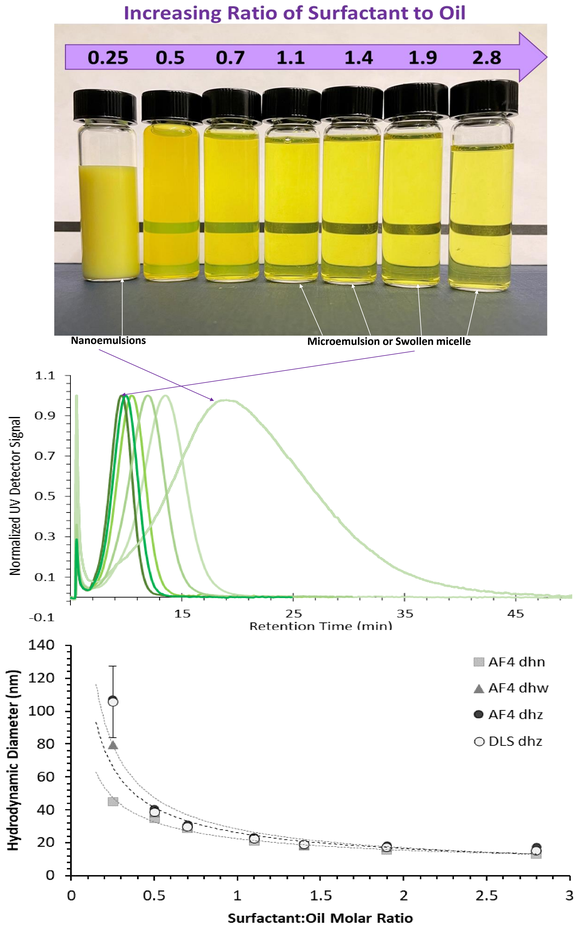

Figure 3. a) Formulations prepared at differing ratios of surfactant to oil, showing the transition of dispersion state from translucent to turbid. **b)** AF4 fractograms overlaying UV-Vis detector signals, showing change in size and PDI as oil content is increased and the system transitions from a microemulsion to nanoemulsion. **c)** Overlay of particle hydrodynamic diameter as determined via batch DLS and AF4-MALS-DLS, with number (n), weight (w), and intensity (z) averages from AF4 distribution.

RESULTS: THERMODYNAMIC VS KINETIC STABILITY

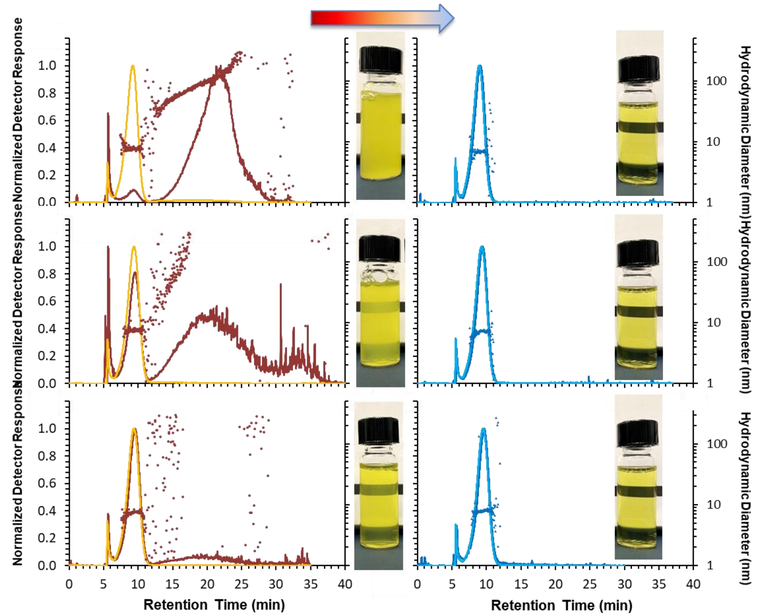

Figure 5. AF4 fractograms for formulation from Figure 4 before and after incubation at 70°C for 30 minutes. UV-Vis detector response (yellow and light blue) with light scattering intensity at 90° from MALS (brown and dark blue) are overlaid with hydrodynamic radius from online DLS (scatter). Insets: Still images of formulations before (left) and after (right). Particle sizes summarized in Table 1.

Table1. Heating Stability Comparison

ID	DLS $(d_h)_z$	AF4 $(d_h)_z$	AF4 $(d_h)_n$	AF4 $(d_h)_z$
1	182.4	171.8	15.8	15.4
2	114.2	93.4	15.4	16.1
3	76.2	70.8	14.2	14.0
		Before Heating		After

**Hydrodynamic diameter in nm.*

- **Use of low shear conditions in the A2O direction produces larger particle sizes with high PDI.**
- **Use of high shear conditions in the A2O direction produces lower particle sizes and PDI.**
- **At the composition of Phytonadione Injection product given enough time and energy the system transitions from a nano- to a microemulsion (thermodynamically favored state).**

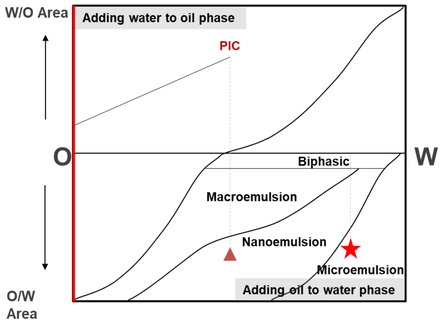

Figure 6. Binary phase diagram for a fixed surfactant to oil ratio. Y-axis incorporates the magnitude of interfacial area generated during the mixing process. For each formulation composition such a diagram exists as a cut-plane through a traditional pseudo-ternary phase diagram, extending the diagram into a third dimension. Construction of an interface directed pseudo-ternary phase diagram can aid in the explanation of variations observed during formulation process. In the A2O direction as the formulation passes through the PIC the amount of shear experienced during interface rearrangement dictates the resultant particle size distribution and polydispersity.

RESULTS: MIXING DIRECTIONALITY EFFECTS

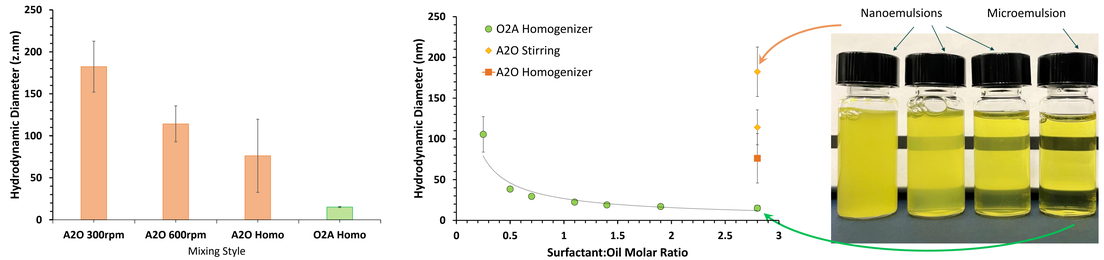

Figure 4. a) Particle sizes for formulations prepared at equivalent composition (surfactant to oil ratio, S:O = 2.8) using different formulation directionality and mixing procedures, **b)** overlaid with Figure 2 batch particle sizes from DLS, with **c)** accompanying representative images.

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